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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,099	01/20/2004	Timothy J. O'Leary	AFIP 03-16 01	4916

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OFFICE OF THE STAFF JUDGE ADVOCATE
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

MAIL DATE	DELIVERY MODE
06/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,099	O'LEARY ET AL.	
	Examiner	Art Unit	
	HEATHER G. CALAMITA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24,26-35,37-39 and 41-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24,26-35,37-39 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/2008*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 16-24, 26-35, 37-39 and 41-46 are currently pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Response to Amendment

The declaration filed on February 12, 2008, under 37 CFR 1.131 has been considered but is ineffective to overcome the Singh et al. and Wu et al. references. Applicants are not able to antedate either of these references because both of these references have publication dates of more than a year before the effective filing date of the instant application. The dates of publication of the prior art references therefore constitute a statutory bar. MPEP 2141.01 states

> A 35 U.S.C. 103 rejection is based on 35 U.S.C. 102(a), 102(b), 102(e), etc. depending on the type of prior art reference used and its publication or issue date. For instance, an obviousness rejection over a U.S. patent which was issued more than 1 year before the filing date of the application is said to be a statutory bar just as if it anticipated the claims under 35 U.S.C. 102(b).

The declaration under 37 CFR 1.132 filed February 12, 2008, is insufficient to overcome the rejection of the claims based upon 35 USC 103 (a) as set forth in the last Office action because: The declaration is not comsenurate in scope with the claims. Applicants' declaration argues methods of making the liposomes as well as a lower limit of detection. Applicants argue the method used by Singh et al. to produce the liposomes is not compatible with DNA encapsulation and that it allows only for passive encapsulation of DNA segments into the liposomes. These arguments are not comsenurate in scope with the claims because the instant claims do not recite any limitations with respect to lipid mixtures or the number of amplicons necessary for the assay. Additionally, Applicants argue the methods of Singh et al. and Wu et al. respectively, are not as sensitive with respect to detection capabilities. Again these arguments are

not comsenurate in scope with the instant claims because there are no limitations requiring a specific level of detection.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 17, 21-28, 31, 33, 35-38, 40, 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS).

With regard to claims 16 and 43, Singh et al. teach a method for immunoliposome assay comprising

a) encapsulating markers within the closed shell liposomal bilayers (see p. 6020 col. 1 lines 16-18 and p. 6021 Figure 2, where the term "closed shell" is not defined in the instant specification therefore the liposomal bilayer of Singh et al. is interpreted to meet this recitation)

b) associating receptors to the extravesicular surface of the liposomal bilayers (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2)

c) exposing the selected receptors to an immobilized target analyte which bind to the liposomal bilayer associated selected receptors (see p. 6021 Figure 2, where the target analyte is the toxin)

d) removing unbound liposomal bilayers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 14-18)

e) lysing the bound liposomal bilayers to release the markers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 18-20)

g) detecting the markers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 20-23).

With regard to claim 17, Singh et al. teach the analyte is a biological toxin (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 1-7)

With regard to claim 20, Singh et al. teach the receptors are gangliosides (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2).

With regard to claims 21-23, Singh et al. teach liposomes provide sites for covalent attachment (see p. 6024 under *Conclusions*. Additionally, the covalent attachment of proteins (and antibodies) to hydrocarbons is well known in the art and within the ability of a skilled artisan to perform).

With regard to claims 24 and 25, Singh et al. teach associating receptors to the extravesicular surface of the liposomal bilayers comprises electrostatically coupling charged receptors to charged lipids in the liposomal bilayers (see p. 6023 under *Nonspecific Binding of Liposomes*, where Singh teaches receptors (ie proteins) can adsorb to liposomes via electrostatic attraction).

With regard to claim 26, Singh et al. teach anchoring integral membrane protein receptors to the liposomal bilayers by direct incorporation into the liposomal bilayer (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2).

With regard to claim 27, Singh et al. teach reducing non-specific binding of the liposomal bilayers on an immobilizing substrate by varying the lipid composition of the lipid bilayer to alter the size of the liposome, the fluidity of the bilayer or the polarity and charge of the surface of the bilayer (see p. 6023 under *Nonspecific Binding of Liposomes*, where Singh teaches liposomes,

depending on their composition and groups present on the outer surface can exhibit non-specific binding).

With regard to claim 28, Singh et al. teach reducing non-specific binding of the liposomal bilayers on an immobilizing substrate by altering the charge density of the surface of the bilayer (see p. 6023 col. 2, where Singh teaches the use of BSA and polystyrene and negatively charged liposomes to reduce non-specific binding).

With regard to claim 32, Singh et al. teach the liposomal bilayers are lysed with Triton X-100 (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 1-7).

With regard to claims 39-41, Singh et al. teach detecting toxins in food (see p. 6024 col. 2, under *Conclusions*, where food monitoring and clinical diagnostics are disclosed).

With regard 42, Singh et al. teach the immobilized target analyte is immobilized on a microtiter plate (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7).

Singh et al. do not teach all of the limitations of the claims, specifically with regard to claims 16 and 43, Singh do not teach step a) encapsulating a plurality of identical nucleic acidsegments within the liposome step f) subsequently amplifying the nucleic acid segments and step g) detecting the released nucleic acids.

With regard to claim 19, Singh et al. do not teach teach using nucleic acids as reporters and amplifying the nucleic acid reporters using PCR, where the nucleic acids comprise 50-1000 identical nucleic acid segments).

With regard to claim 34, Singh et al. do not teach detecting with gel electrophoresis.

With regard to claim 33, Singh et al. do not teach the nucleic acid segments are amplicons that are amplified using PCR.

With regard to claim 35, Sing et al. do not teach the amplifying and detecting are coupled.

With regard to claim 36, Singh et al. do not teach detecting 10-1000 molecules of the analyte.

With regard to claim 37, Singh et al. do not teach detecting the analyte at subattomolar quantities.

With regard to claims 16 and 43 step a), Wu et al. teach using nucleic acids as reporters for amplification, f) amplifying the nucleic acids and g) detecting the nucleic acids as an indication of the presence of the analyte (see p. 322 col. 2 under Immuno-PCR assay lines 9-28 and p. 323 Figure 1).

With regard to claim 19, Wu et al. teach using nucleic acids as reporters and amplifying the nucleic acid reporters using PCR, where the nucleic acids comprise 50-1000 identical nucleic acid segments (see p. 322 col. 2 under Immuno-PCR assay lines 9-28, once the reporter is amplified there will be greater than 1000 nucleic acid segments).

With regard to claim 33, Wu et al. teach the nucleic acids are amplified using PCR (see p. 322 col. 2 under Immuno-PCR assay lines 9-28).

With regard to claim 34, Wu teaches detecting with gel electrophoresis (see p. 322 col. 2 under *Immuno-PCR assay*).

With regard to claim 35, Wu et al. teach the amplifying and the detecting are coupled (see p. 322 col. 2 under *Immuno-PCR assay*, where amplification occurred and the products were detected by gel electrophoresis).

With regard to claim 36, Wu teaches detecting 10-1000 molecules of the analyte (see the abstract)

With regard to claim 37, Wu teaches detecting the analyte at subattomolar quantities (see the abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "…the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

4. Claims 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in further view of Cao et al. (The Lancet, 2000).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claim 18.

With regard to claim 18, Cao teach the use of an assay (immuno PCR) to spatially localize an analyte within a fixed tissue section (see the abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and apply the method to in situ detection as taught by Cao in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods in a fixed tissue sample. Cao teaches a technique which uses the amplification of DNA markers is useful in situ because it allows for

the detection of antigens or target analytes at low levels in in-tact cells or tissue sections (see p. 1002 paragraph bridging col. 1 and 2). A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and applying the method to in situ analysis in order to detect of antigens or target analytes at low levels in in-tact cells or tissue sections.

5. Claims 20, 42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) as applied to claim 16 above and in further view of Bernstein (USPN 4,704,355).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 20, 42 and 46.

With regard to claims 20 and 46, Bernstein teaches the receptors a re monoclonal or polyclonal antibodies (see col. 4 line 24).

With regard to claim 42, Bernstein teaches a particle (see col. 5 line 34).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies.

Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and use antibodies as the receptors as taught by Bernstein in order to detect the presence of a variety of analytes samples with greater sensitivity than possible with standard immunoassay and fluorescence detection methods in a fixed tissue sample. Bernstein teaches that antibodies can be successfully used as receptors in liposome assays (see col. 4 lines 21-26). A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and using antibodies as the recptors as taught by Bernstein in order to detect the presence of a variety of analytes in a specific binding interaction.

6. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in view of Boxer et al. (USPN 6,503,452 B1).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 29-30.

With regard to claims 29-30, Boxer et al. teach reducing non-specific binding by varying the spacer arm (see col. 14, line 8-12, where the spacer arm is polyethylene glycol).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. and Wu et al. with the PEG arm, as taught by Boxer et al. in order to immobilize the liposome while reducing non-specific binding. Boxer et al. teaches that a PEG spacer arm is an acceptable way to immobilize liposomes. An ordinary practitioner would have been motivated to use the immunoliposome assay as taught by Singh et al. and Wu et al. with the PEG arm, as taught by Boxer et al. in order to successfully immobilize the liposome and reduce non-specific binding.

7. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in view of in view of Huang et al. (Biotechniques, 1996).

The teachings and suggestions of Singh et al. and Wu et al. are described previously. Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 31. Huang et al. teach removal of contaminating DNA with DNase (see the abstract)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. and Wu et al. with DNase for the removal of contaminating DNA, as taught by Huang et al. in order to remove any contaminating DNA which could result in inaccurate results. Huang et al. teaches that DNase removes contaminating DNA (see abstract). An ordinary practitioner would have been motivated to use the immunoliposome assay as taught by Singh et al. and Wu et al. DNase, as taught by Huang et al. in order to successfully remove contaminating DNA from the assay and achieve more accurate results.

8. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) as applied to claim 16 above and in further view of Beebe et al. (US 2004/0258570).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claim 32.

With regard to claim 32, Beebe et al. teach lysing the liposomes with melittin (see paragraph 0036).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would

expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and melittin as a lysing agent as taught by Beebe et al. in order to lyse the liposomes. Beebe et al. teach melittin is an effective lysing agent for liposomes (see paragraph 0036). A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and melittin as a lysing agent as taught by Beebe et al. in order to effectively lyse the liposomes.

9. Claims 34 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) as applied to claim 16 above and in further view of Wu (US 2005/0079520).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 34 and 39.

With regard to claim 34, Wu teaches capillary electrophoresis (see paragraph 0014).

With regard to claim 39, Wu teaches detecting analytes in water (see paragraph 0155).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "…the method described here demonstrates that immuno-PCR technology greatly

extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and capillary electrophoresis for detection as taught by Wu in order to efficiently detect the amplification products. Wu teaches capillary electrophoresis is an efficient means of detection for amplification products (see paragraph 0014). A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and capillary electrophoresis as taught by Beebe et al. in order to effectively detect the amplification products of the assay.

10. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology,

2001, cited in the IDS) as applied to claims 16 and 43 above and in further view of Bailey et al. (Biochimica et Biophysica Acta, 2000).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 44 and 45.

With regard to claims 44 and 45, Bailey et al. teach mixing phospholipid single shell vesicles with ethanol and calcium chloride to form phospholipids-nucleic acid segment complexes and dialyzing the complexes (see p. 242 col. 1 under 2.4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "…the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and mixing phospholipid single shell vesicles with ethanol and calcium chloride to form phospholipids-nucleic acid segment complexes and dialyzing the complexes as taught by Bailey et al. in order to entrap DNA. A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and mixing phospholipid single shell vesicles with ethanol and calcium chloride to form phospholipids-nucleic acid segment complexes and dialyzing the complexes as taught by Bailey et al. in order to effectively entrap DNA within the liposome.

Response to Arguments

12. Applicants' arguments filed February 12, 2008, have been fully considered but they are not persuasive. Applicants' arguments with respect to the 103 (a) rejections over Singh et al. and Wu et al. are directed to arguments outlined in the declarations filed. These arguments are not persuasive for reasons discussed above. Applicants' arguments with respect to the remaining 103 (a) rejections are moot in view of the explanation of the insufficiency of the filed declarations.

Summary

13. No claims were allowable.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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